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SPECIAL ARTICLE

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Designing and conducting a randomized trial for pandemic critical illness: the 2009 H1N1 influenza pandemic

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Abstract *Purpose:* To analyze the hurdles in implementing a randomized trial of corticosteroids for severe 2009 H1N1 influenza infections. *Methods:* This was an investigator-led, multicenter, randomized, placebo-controlled, double-blind trial of corticosteroids in ICU patients with 2009 H1N1 influenza pneumonia requiring mechanical ventilation. The feasibility of and hurdles in designing and initiating a phase III trial in a short-lived pandemic crisis were analyzed. The regulatory agency and ethics committee approved the study's scientific, financial, and ethical aspects within 4 weeks. Hydrocortisone and placebo were prepared centrally and shipped to participating hospitals within 6 weeks. The inclusion period started on November 9, 2009. *Results:* From August 1, 2009 to March 8, 2010, only 205/224 ICU patients with H1N1 infections required mechanical ventilation. The peak of the wave was missed by 2–3 weeks and only 26 patients were randomized. The two main reasons for non-inclusion were patients' admission before the beginning of the trial and ICU personnel overwhelmed by clinical duties. Parallel rather than sequential regulatory and ethics approval, and preparation and masking of study drugs by local pharmacists would have allowed the study to start 1 month earlier and before the peak of the "flu" wave. A dedicated research team in each participating center would have increased the ratio of screened to randomized patients. *Conclusion:* This report highlights the main hurdles in implementing a randomized trial for a pandemic critical illness and proposes solutions for future trials.

Keywords Pandemic crisis · Clinical trial · Design · Ethics · H1N1 · Critical illness

Introduction

The 2009 H1N1 influenza caused over 18,449 deaths worldwide [1], primarily in young people [1–3] who developed uncontrolled lung and systemic inflammation [4, 5]. Apart from vaccines and other preventative measures, neuraminidase inhibitors are the only treatment and the development of adjunctive therapies is an unmet need [3]. However, there are no recommendations for the design and conduct of randomized trials in pandemic critical illness. This paper suggested recommendations for pandemic research based on the experience from a multicenter randomized trial performed in ICU patients with 2009 H1N1 influenza.

Study design and conduct

Definition of the clinical question

Patients with H1N1 influenza infection died primarily from acute respiratory distress syndrome (ARDS) though they were receiving treatment with neuraminidase inhibitors [3]. The International Forum for Acute Trialists (InFACT) identified corticosteroids and statins as readily available drugs with strong biological rationale to be investigated as adjunctive therapies for H1N1 patients admitted to ICU [6]. Corticosteroids may improve survival in ARDS patients [7, 8]. They were used in 50–69% of ICU patients with H1N1 [9, 10], and decreased circulating levels of inflammatory mediators and improved gas exchange and organ dysfunction [11]. Then, the benefits to risk of corticosteroids were evaluated in the low doses corticosteroids as adjuvant therapy for the treatment of severe H1N1 flu (CORTIFLU) study, which was endorsed by InFACT [6].

Choice of study design

This was a prospective, multicenter, randomized, placebo-controlled, double-blind trial on two parallel groups. It was preceded by a prospective observational study, which started on July 1, 2009, and ended with activation of the randomized controlled phase.

Choice of study population

As young people were more likely to be sicker [9–12], ICU patients aged of 15 or more with strong suspicion or proven H1N1 infection, diffuse alveolar pneumonia, and receiving invasive or noninvasive mechanical ventilation were eligible. As early administration may increase corticosteroids' efficacy [7, 8], patients were included within a 96-h time-window. Each patient's informed consent or surrogate decision maker's assent was obtained prior to inclusion whenever possible; otherwise only the patient's deferred consent was recorded. Exclusion criteria were pregnancy, life expectancy of less than 1 month, moribund patient, confirmed viral encephalitis or myocarditis, previous use of corticosteroids at a dose of 30 mg per day of prednisone or equivalent for more than 1 month, any acute conditions for which corticosteroids could be indicated (e.g., severe asthma, acute exacerbation of chronic obstructive pulmonary disease (COPD), Addison's crisis), and antiviral treatment for more than 5 days.

Choice of study interventions

Type, dose, and duration of corticosteroids were based on prior systematic reviews [7, 8] and one observational study in adults with 2009 H1N1 influenza [11]. Hydrocortisone was administered as a 50 mg intravenous bolus every 6 h for 7 days, tapered to 50 mg every 12 h from day 8 to day 14 post-randomization and to 50 mg every 24 h from day 15 to day 21 (or up to hospital discharge depending which event occurred first). Co-interventions were harmonized across centers (Supplemental Table 1).

Randomization and blinding

Randomization (in a 1:1 ratio) used a computerized random-number generator list and permutation blocks, and was centralized through a secure website. Study drugs were sealed in sequentially numbered, identical boxes that contained the entire treatment for each patient. The sequence was concealed from patients, medical and nursing staff members, pharmacists, investigators, and members of the monitoring board. Hydrocortisone was prepared in vials containing 100 mg of hydrocortisone hemisuccinate powder with ampules containing 2 ml of sterile water diluent (SERB, Paris, France). The vials containing placebo or hydrocortisone were coded and masked centrally, and then shipped to participating sites (Unité des essais cliniques, AGEPS, Paris, France).

Choice of follow-up

The following data were recorded at baseline: demographic and anthropometric data, co-morbid conditions; vital signs, SAPSII [13], and SOFA score [14]; interventions, including mechanical ventilation, extracorporeal membrane oxygenation (ECMO), antibiotics and antiviral treatments; hematologic, chemical data and blood gas analyses; viral RNA detection by real-time reverse transcriptase polymerase chain reaction on nasopharyngeal swabs or on bronchoalveolar lavage fluids; and microbial cultures from blood and bronchial aspirate.

Patients were followed up to hospital discharge for vital signs, results from laboratory tests and cultures of specimens drawn from respiratory tract and any new site of infection, and for any major interventions. Vital and functional status was also recorded at 6 months.

Choice of study end points

The primary end point was in-hospital mortality. Secondary end points included death rates at 28, 90, and 180 days, proportion of patients receiving ECMO, number of mechanical ventilation and ICU free days, length of stay, and respiratory function and health status at day 180. Safety was assessed by recording adverse events, particularly superinfection, gastrointestinal bleeding, and clinical muscular weakness.

Sample size calculation and statistical analysis plan

For estimation of a reasonable magnitude of treatment effect with corticosteroids, and in the absence of data specific to H1N1, information from a recent systematic review on corticosteroids for ARDS was used [7]. A sample size of 438 patients was needed to achieve a statistical power of 80% to detect an absolute decrease in mortality of 10% from an existing death rate of 20% [2, 9, 10, 12].

Intent-to-treat analyses and use of R 2.6.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria) were planned. In-hospital mortality was estimated by considering alive at discharge as a competing event [15]. Cumulative incidence of hospital mortality was computed (http://biowww.dfci.harvard.edu/~gray/cmprsk_2.1-4.tar.gz). Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were computed using Cox proportional cause-specific hazard models. Mortality at 28, 90, and 180 days was estimated by crude ratios with logistic regression models. Cumulative incidence of weaning from mechanical ventilation was computed with death as a competing risk event. Mean length of stay was compared by Student's *t* test or non-parametric Wilcoxon rank sum tests (as appropriate). Exploratory analyses were restricted to the primary outcome to assess heterogeneity in treatment effects according to age and type of mechanical ventilation (noninvasive, invasive). A *p* value of 0.05 or less in a two-sided test was set as significant.

Study organization and funding

This was an investigator-led trial. In August 2009, in order to fund the trial the French Ministry of Health required independent evaluation of the scientific merits and financial appropriateness of the project. After funding approval, the study protocol and qualifications of all investigators had to be approved by one *Comité de Protection des Personnes* (i.e., centralized approval by an ethics committee). Owing to the pandemic context, fast-track procedures for scientific, financial, and ethical evaluations of the study protocol were granted.

Table 1 Organization of a randomized trial in pandemic critical illness

	What was done?	How long did it take?	How could it be better?	Estimated time saving
Initiative	Investigators led trial	About 4 weeks	Investigators networks should be prepared in advance to launch future pandemic research	4 weeks
Scientific evaluation of the protocol	Independent evaluation by Institute of Microbiology and Infectious Diseases (part of INSERM)	4 weeks' fast-track process	Scientific evaluation should have been anticipated Reviews should have taken no longer than 1 week	3 weeks
Financial evaluation and sponsoring	Independent evaluation by Department for Clinical Research and Development (AP-HP)	3 days' fast-track process	Unlikely to be shorter	–
Ethical evaluation	Independent evaluation by Comité de Protection des Personnes Saint Germain en Laye	3 weeks' fast-track process	Ethical evaluation should have been anticipated Reviews should have taken no longer than 1 week Ethical evaluation should have been run in parallel to the scientific evaluation	3 weeks
Study treatments	Centralized preparation of active treatment and placebo and labeling	6 weeks' fast-track process	Local preparation of active treatment and placebo using commercially available drugs	5 weeks
Activation of study sites	Study materials and drugs were shipped via express mail and conference calls were organized to review all study materials with local investigators and pharmacists 39 sites were activated in 3 consecutive waves	3 weeks	All sites should be activated in one single wave Conference calls worked very well	2 weeks
Assistance for workload associated with patients enrolment	We provided the investigators with technical assistance for completing electronic CRF	–	A dedicated research team should be provided to each study site	–

INSERM national institute for health research, *AP-HP* assistance publique hôpitaux de Paris, *CRF* case report form

Results

Study organization, funding, and dates

The study protocol was endorsed by investigators from 39 ICUs in September 10, 2009, approved for scientific aspects by the Institute of Microbiology and Infectious Diseases (part of the national institute for health research INSERM) on October 10, for financial aspects by the Department for Clinical Research and Development (AP-HP) on October 13, and for ethical aspects (including waiver of consent and deferred consent) on November 3 (Table 1). On November 3, the study was launched (P090902). Deferred approval for the observational study was obtained.

Sites were activated in three consecutive waves (November 9 and 19, and December 1) according to geographical weekly incidence of H1N1 hospitalized cases in France. Study drugs were prepared within 4 weeks (October 21) (Table 2). Two additional weeks were needed for setting up centralized randomization facilities and a web-based CRF, and for treatments' labeling and shipping. All study materials were reviewed with investigators via conference calls on the day study drugs were delivered to their pharmacy, and during face to face meeting the following week.

Patients' enrolment

The trial was suspended on March 15, 2010 due to the pandemic end. Centers were kept 'active' through the 2010 flu season, and the study was stopped on February 23, 2011. From July 1, 2009 to March 8, 2010, 224/247 ICU patients had confirmed H1N1 pneumonia (Fig. 1). A total of 105/205 (51%) mechanically ventilated patients were admitted on average 29 days before the randomization phase (median −24 days; IQR −35, −15; Fig. 2). The trial started 1 week, 2 days, and 3 weeks after the peak of the flu wave in the first, second, and third groups of centers, respectively (Fig. 2). Twenty-six of 100 patients screened during the randomization period were included (Fig. 1). The main reason for non-inclusion was limited staff resources (Table 3). Nine ICUs received no patient and nine received more than 10 patients (for a total of 122 patients). These busy ICUs were unable to include more than 2 patients simultaneously, except one in which there was a dedicated research team. There were 39/205 (19%) in-hospital deaths.

Table 2 Study design in pandemic critical illness

	What was done?	How could it be better?	Comments
Experimental plan	Randomized trial on 2 parallel groups	2 × 2 factorial design allowing concomitant evaluation of neuraminidase inhibitors	Indeed this would have avoided competition with concomitant trials in participating sites
		Bayesian adaptive design	Adaptive design would permit evaluation of multiple interventions in the same trial and by integrating information from patients enrolled early in the trial may adjust allocation to the more favorable treatment arm. This design may allow both the number of patients to be included and the duration of the study to be reduced
Randomization	Centralized through secure website	–	There was no report of failure to include a patient related to the use of centralized randomization
Blinding	Double-blind trial—masking of treatment done centrally	Local pharmacist masking study treatments	This would likely have allowed the trial to start a month sooner
Primary end point	In-hospital mortality	ICU free days and hospital mortality	Indeed in the pandemic context and the burden on ICU beds, it is important that treatments shorten survivors' ICU length of stay
Sample size calculation	Baseline risk based on actual H1N1 death rates among ICU patients	–	Observed death rates matched expected death rates
	Estimated treatment benefits based on indirect evidence, i.e., systematic reviews on corticosteroids for all cause ARDS	Bayesian adaptive design approach	The total number of patients with severe H1N1 pneumonia was about half of the expected sample size
	Frequentist approach		Given the uncertainty on the crude incidence of the disease in a geographic area, and the potential need to evaluate multiple interventions, adaptive design may be the preferred method

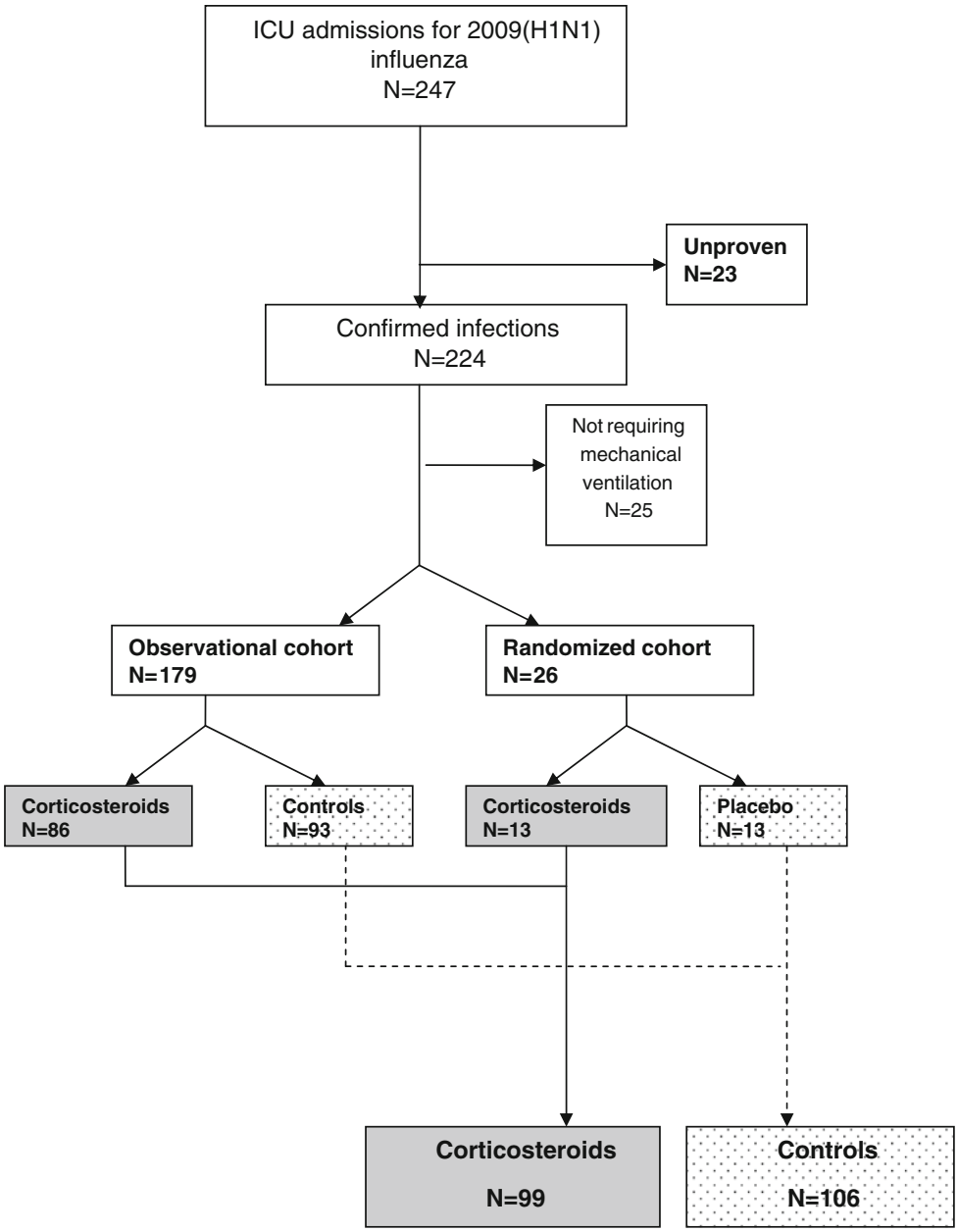

Fig. 1 Trials flow chart

Discussion

This randomized trial evaluating a drug therapy for a pandemic critical illness failed to recruit an appropriate number of patients.

The proportion of research participants among eligible patients (25%) was in keeping with previous trials [16, 17]. In the observational study, 48% of patients were treated with corticosteroids highlighting the equipoise among investigators. More than half of eligible patients were treated in less than one-third of participating ICUs. In these ICUs, staff members were overwhelmed with clinical duties limiting their availability for randomizing multiple patients the same week. Such a pandemic-related extreme workload on ICU staff was predictable [12] and highlighted the need for dedicated research teams.

Though there were only 2 months from study design to inclusion of the first patient, several measures may have permitted one to launch the trial before the peak of the flu wave. First, the regulatory agency and ethics committee approved the study in 4 weeks compared to 1 year in a nonpandemic context [16, 17]. However, French regulations required that scientific and financial approvals preceded submission of the study protocol to the ethics committee. Parallel

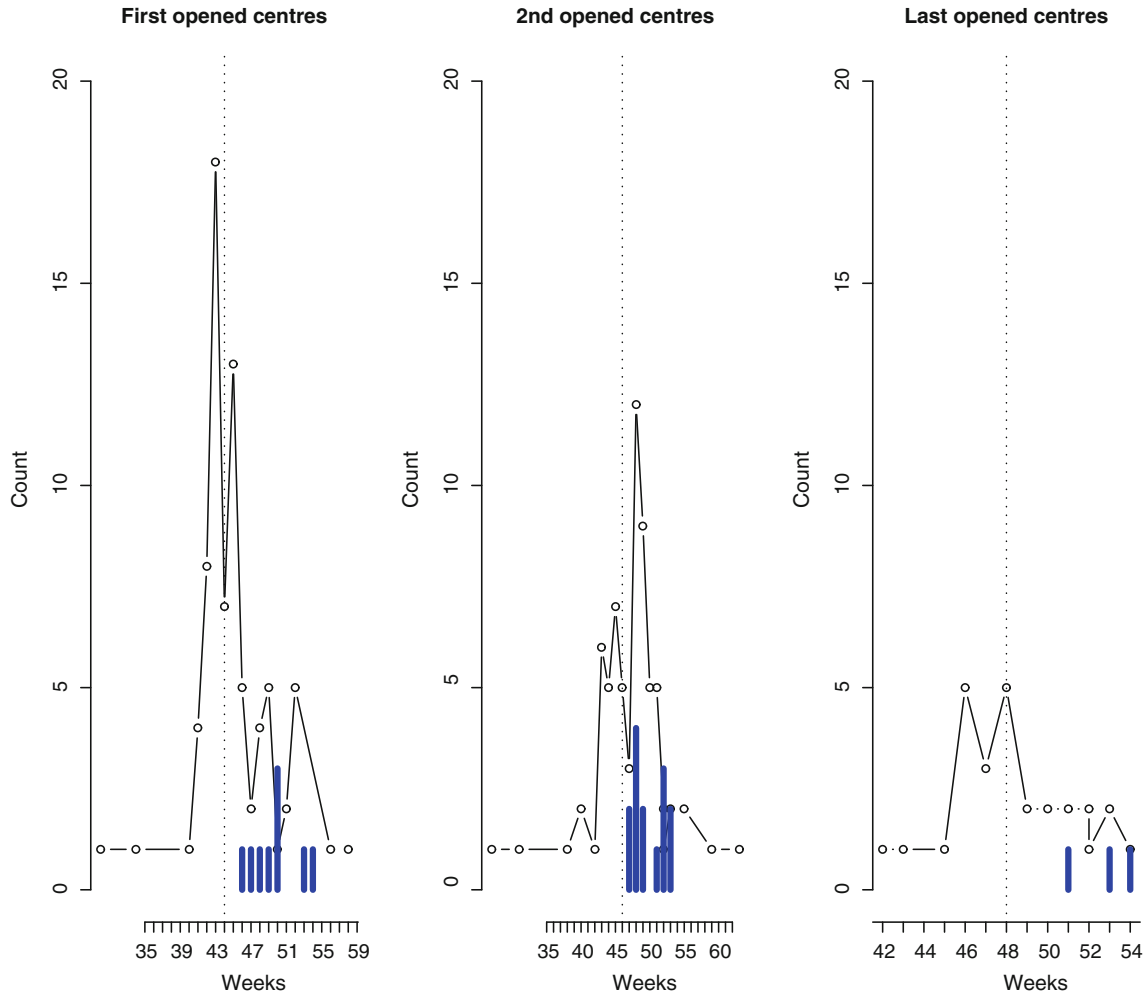

Fig. 2 Number of new cases of H1N1 influenza-related acute lung injury/acute respiratory distress syndrome, each week, in the first (*left panel*), second (*middle panel*), and third (*right panel*) set of ICUs activated in the randomized period. The *blue bars* represent randomized patients. The *dotted vertical lines* indicate the date of activation of centers in the randomization period

scientific, financial, and ethical evaluations of the protocol could have shortened the delay to enroll patients by 3 weeks. Alternately, regulatory agencies and the ethics committee may give prior approval to protocols prepared by investigator networks [6]. Second, the use of open-labeled hydrocortisone may have avoided the 6 weeks' required to provide centers with study drugs. Though some authors suggested that if mortality is the primary outcome non-blinded trials are valid [18], confounding factors like co-interventions may be seriously affected resulting in fatal biases [19]. Third, commercially available drugs may have been masked by local pharmacists as in previous multicenter trials [16, 20]. In future pandemic research, commercially available drugs should be compounded at local hospital pharmacies so long as acceptable placebos can be as well.

The observed mortality of 19% matched the expected mortality [2, 9–12], highlighting an efficient dissemination of epidemiological data during the 2009 H1N1 pandemic. By contrast, the actual incidence of ICU cases was much lower than expected. There were 987 ICU patients aged 15 years old or more in France as of April 6, 2010 (http://www.invs.sante.fr/…/grippe_dossier/…grippe/…/Bulletin_grippe_260111.pdf). Sixty-six were pregnant women and roughly half of them had underlying respiratory diseases such as asthma. In the 39 participating ICUs, the crude number of H1N1 patients was half of the calculated sample size. Such discrepancy between expected and observed incidence rates was not infrequent in epidemic diseases [21], illustrating the challenge to obtain an adequately powered trial during short-lived epidemics. Because of the unpredictable incidence rate, Bayesian approaches may be more appropriate for

Table 3 Reason for non-inclusion in the randomized trial

	Number of patients with reason for non-inclusion[a]
Prior to initiation of the randomized trial	105
Limited ICU staff resources	45
Pregnancy	4
Life expectancy of less than 1 month, moribund patient	2
Multiple organ failure	7
Confirmed viral encephalitis or myocarditis	1
Severely immunosuppressed	9
Previous corticosteroids at a dose of 30 mg per day of prednisone or equivalent for 1 month or more	7
Any indication requiring corticosteroids (e.g., severe asthma, acute exacerbation of COPD, Addison's crisis)	3
Treatment with antiviral drug for more than 5 days	3
Participating in another trial	5

[a] Patients could have more than one reason

pandemic research than standard statistical approaches. They allow one to incorporate information from regions already affected by the disease in defining a priori treatment benefit [22]. Bayesian adaptive designs allow simultaneous evaluation of multiple interventions, and by integrating treatment responses in patients enrolled early in the trial, they allow one to adapt the allocation to interventions with higher probability of efficacy [23].

In conclusion, although it was possible to obtain fast regulatory and ethical approvals and funding of the trial, and to motivate a high number of ICUs, it was not possible to complete an adequately powered trial. The low recruitment resulted mainly from a delayed initiation of the trial (i.e., after the peak of the "flu" wave). This could have been prevented by parallel rather than sequential regulatory and ethical approvals, use of commercial rather than 'study-specific' drugs, local versus centralized masking of study drugs, and dedicated research teams. Finally, given the unpredictable incidence of cases and the need for investigating multiple interventions and getting information on treatment efficacy and safety in a timely fashion, future pandemic research should consider following an adaptive design.

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Appendix

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